# EXHIBIT 1

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | |
|---|---|
| BIOVAIL LABORATORIES INTERNATIONAL SRL a corporation of Barbados,<br><br>Plaintiff,<br><br>v.<br><br>ANDRX PHARMACEUTICALS, LLC and ANDRX CORPORATION,<br><br>Defendants. | C.A. Nos. 05-586-KAJ (consolidated case)<br><br>**FILED UNDER SEAL PURSUANT TO D. DEL. LR 26.2** |

**DECLARATION OF STEVEN MADDOX IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT OF U.S. PATENT NO. 5,529,791**

I, Steven Maddox, hereby declare:

1. I am an attorney at Foley & Lardner LLP, counsel for plaintiff Andrx Pharmaceuticals, LLC, and Andrx Corporation ("Andrx") in this action.

2. My business address is 3000 K St. N.W., Suite 500, Washington, DC, 20007-5143.

3. I make this declaration in support of Andrx's Motion for Summary Judgment of Non-Infringement of U.S. Patent No. 5,529,791.

4. Exhibit A to this declaration is a true and accurate copy of *Biovail Corp. Int'l. v. Andrx Pharmaceuticals, Inc.*, 158 F.Supp.2d 1318 (S.D.Fla. 200).

5. Exhibit B to this declaration is a true and accurate copy of *Biovail Corp. Int'l. v. Andrx Pharmaceuticals, Inc.*, 239 F.3d 1297 (Fed. Cir. 2001).

6. Exhibit C to this declaration is a true and accurate copy of U.S. Patent No. 5,529,791.

7. Exhibit D to this declaration is a true and accurate copy of the Brief Of Plaintiffs- Appellants Biovail Corporation International, Biovail Laboratories, Inc. and Galephar P.R., Inc. Ltd., filed in *Biovail Corp. Int'l. v. Andrx Pharmaceuticals, Inc.*, 239 F.3d 1297 (Fed. Cir. 2001).

8. Exhibit E to this declaration is a true and accurate copy (without exhibits) of the Expert Report of Gerald S. Brenner, Ph.D., Regarding Andrx's Infringement of the '791 Patent, served by Biovail in this action.

9. Exhibit F to this declaration is a true and accurate copy (without exhibits) of the Affirmative Expert Report of Martyn C. Davies, Ph.D., served by Biovail in this action.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: 11/29/06

Steven A. Maddox

# EXHIBIT A

and the stipulation before the Court, the Court finds that Claimant's stipulation by affidavit sufficiently protects Petitioners' right to limit their liability, allowing the Court to lift its stay order. Accordingly, Claimant's Motion to Lift Stay Order is **GRANTED.**


**BIOVAIL CORPORATION INTERNATIONAL, et al., Plaintiffs,**

**v.**

**ANDRX PHARMACEUTICALS, INC., Defendant.**

**No. 98–7096–CIV.**

United States District Court, S.D. Florida.

March 6, 2000.

Licensees of patent for hypertension drug sued generic drug manufacturer for infringement. The District Court, Dimitrouleas, J., held that: (1) patent was not literally infringed, and (2) patent was not infringed under doctrine of equivalents.

Judgment for defendant.

Affirmed at 239 F.3d 1297.

**1. Patents ⇐314(5)**

It is court's role to construe claims of disputed patent.

**2. Patents ⇐165(1), 167(1), 168(2.1)**

Court construing patent claim language principally looks to claims themselves, specifications, and prosecution history.

**3. Patents ⇐159**

Court construing patent claim only looks to extrinsic evidence, such as expert affidavits or declarations, if intrinsic evidence is ambiguous.

**4. Patents ⇐226.6**

In order for accused product to literally infringe patent claim, each and every element must be found in accused product exactly.

**5. Patents ⇐312(4)**

Burden to show literal infringement is on patentee by preponderance of evidence.

**6. Patents ⇐250**

Patent for extended release composition for drug diltiazem was not literally infringed by accused product, which did not contain homogeneous, dry state admixture of drug and wetting agent.

**7. Patents ⇐237**

Doctrine of equivalents is sometimes applied in patent cases to enable patent to cover products not within literal scope of claims if product only differs insubstantially from claim language.

**8. Patents ⇐237**

One way to show insubstantial difference, for purpose of establishing patent infringement under doctrine of equivalents, is to show that substituted element provides substantially same functions in substantially same way to achieve substantially same result.

**9. Patents ⇐312(4)**

Burden to show infringement under doctrine of equivalents is on patentee by preponderance of evidence.

**10. Patents ⇐168(2.1), 237**

In making doctrine of equivalents analysis, scope of equivalents to which patent claim may be allowed is limited by doctrine of prosecution history estoppel.

**11. Patents ⇐168(2.1), 237**

Under doctrine of "prosecution history estoppel," actions taken by patentee during prosecution history act as legal limits on application of doctrine of equivalents by excluding from range of equivalents subject matter surrendered during prosecution of application for patent; estoppel may arise from matter surrendered as result of amendments to overcome patentability rejections, or as result of argument to secure allowance of claim.

See publication Words and Phrases for other judicial constructions and definitions.

**12. Patents ⇐165(2), 237**

Patentee is not entitled to greater rights under doctrine of equivalents than he would be under language of patent claims.

**13. Patents ⇐168(2.1), 237**

Unequivocal assertions or arguments made during prosecution of patent create estoppel which bars application of doctrine of equivalents.

**14. Patents ⇐168(3)**

Patent applicant who has limited claims of patents for controlled release drug formulation primarily in consideration of obviousness rejection is thereafter estopped from asserting relinquished claim scope against defendant under theory of infringement by equivalents.

**15. Patents ⇐168(2.1), 237**

Statements made during prosecution of patent bar patentee from asserting doctrine of equivalents infringement against accused product, regardless of whether statements were required to distinguish prior art, where reasonable competitor could conclude from statements that patentee disclaimed subject matter at issue in order to obtain issuance of patent.

**16. Patents ⇐168(2.1)**

For prosecution history estoppel to apply, assertions in favor of patentability must evince clear and unmistakable surrender of subject matter.

**17. Patents ⇐168(3), 251**

Patent for extended release composition for drug diltiazem was not equivalently infringed by proposed generic equivalent, which used "building up" process from inert sugar core rather than claimed homogeneous, dry state admixture of drug and wetting agent; "building up" process was specifically surrendered during patent prosecution in order to overcome prior art objection.

**18. Patents ⇐237**

Doctrine of prior art estoppel provides legal limitation on application of doctrine of equivalents by mandating that asserted range of equivalents may not encompass prior art at very point at which claims distinguish from that art.

**19. Patents ⇐16.5(1), 237**

Doctrine of prior art estoppel prevents doctrine of equivalents from expanding scope of patent claims to protect subject matter in, or obvious in light of, prior art.

---

Alan M. Grimaldi, Richard H. Kjeldgaard, Mark R. Buscher, Elaine T.L. Wu, Howrey Simon Arnold & White, Washington, DC, Benedict Paul Kuehne, Sidney Katz, Eric C. Cohen, Kathleen A. Rheintgen, Charles Krikorian, Sale & Kuehne, Miami, FL, for Biovail Corporation International, plaintiff.

Alan M. Grimaldi, Richard H. Kjeldgaard, Eric C. Cohen, Kathleen A. Rheintgen, Charles Krikorian, Sale & Kuehne, Miami, FL, for Biovail Laboratories, Inc., plaintiff.

Benedict Paul Kuehne, Sidney Katz, Eric C. Cohen, Kathleen A. Rheintgen,

Charles Krikorian, Sale & Kuehne, Miami, FL, for Galephar P.R., Inc., Ltd., plaintiff.

## FINDINGS OF FACT AND CONCLUSIONS OF LAW

DIMITROULEAS, District Judge.

THIS CAUSE came on for non-jury trial on January 24, January 31, February 14, February 15 and February 16, all in the year 2000. The Court has carefully considered the arguments of counsel, the evidence presented, and the testimony of the witnesses. The Court has also determined the credibility of witnesses and is otherwise fully advised in the premises.

Pursuant to Rule 52(a) of the Federal Rules of Civil Procedure, the Court makes the following Findings of Fact and Conclusions of Law.

1. Plaintiff, Biovail Corporation International, is an Ontario Canada corporation with its principal place of business at 2488 Dunwin Dr., Mississauga, Ontario, Canada L5L IJ9.

2. Plaintiff, Biovail Laboratories, Inc., is a Barbados corporation with its principal place of business at Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, West Indies.

3. Plaintiff, Galephar P.R., Inc., is a Puerto Rico corporation with its principal place of business at Carolina, Puerto Rico 00984–33468.

4. Defendant, Andrx Pharmaceuticals, Inc., is a Florida corporation with its principal place of business at 4001 S.W. 47th Avenue, Fort Lauderdale, Florida 33314.

5. Galephar P.R., Inc. is the owner of United States Patent No. 5,529,791 ("the '791 patent").

6. Biovail Corporation International is the exclusive licensee of Galephar P.R. Inc. under the '791 patent.

7. Biovail Laboratories, Inc. is a wholly owned subsidiary of Biovail Corporation Inc.

8. The alleged act of infringement constituted the filing by Defendant (hereinafter "Andrx") of an Abbreviated New Drug Application (hereinafter "ANDA") with the Food and Drug Administration (hereinafter "FDA") for permission to sell a bioequivalent formulation to the brand name drug Tiazac®.

9. Shortly after filing the ANDA on June 22, 1998, Andrx served Biovail with its paragraph IV certification stating that the formulation described in the ANDA did not infringe the '791 patent which Biovail had listed in the FDA Orange Book as covering the Tiazac® product and that the claims of the '791 were invalid.

10. On October 7, 1998, Biovail filed the present action against Andrx alleging infringement of the '791 patent under 35 U.S.C. 271(e)(2)(a).

### CLAIM INTERPRETATION

11. The invention claimed by the '791 patent provides for an extended-release composition for the drug diltiazem.

12. Diltiazem is a well known drug compound which itself is no longer the subject of an extant patent.

13. Diltiazem is generally prescribed for its calcium channel blocking properties, and, therefore, is useful in the treatment of angina and/or hypertension; either alone or in combination with other medications.

14. The '791 patent contains four claims. Col. 8, line 59 to col. 10, line 11 of '791 patent (Defendant's Exhibit 1).[1]

15. Claim 1 of the '791 patent states:

1. Hereinafter, "DX" or "Def.Exh." will refer to Defendant's Exhibits.

1. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically acceptable adjuvant, and wherein the wetting agent is selected from the group consisting of sugars, $C_{12}$–$C_{20}$ fatty acid esters of sucrose, or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

Col. 8, line 59 to col. 9, line 13 of '791 patent (DX1).

16. In Claim 1, the core of the '791 patent is claimed as containing two components:

(a) an effective amount of the drug diltiazem or salt thereof as the active ingredient;

in admixture with

(b) an effective amount to maintain the solubility of the diltiazem in each bead and to ensure that the solubility of diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions, of one of a number of specifically listed wetting agents, namely, sugars, $C_{12}$–$C_{20}$ fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins, and combinations thereof.

Col. 8, line 59 to col. 9, line 13 of '791 patent (Def.Exh.1).

17. All of the four claims of the '791 patent clearly require the two components of the core, i.e., the diltiazem and the wetting agent, to be in admixture. Col. 8, line 67 to col. 10, line 10 of '791 patent (Def.Exh.1).

*The '791 Patent Specification*

18. The specification of the '791 patent supports the requirement that the wetting agent be in admixture with the diltiazem in the dry state.

19. The '791 patent specification describes two methods for preparing the diltiazem beads.

The patent states as follows:

A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Col. 4, lines 26–30 of the '791 patent (DX1).

20. The patent specification further states that:

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersions or solution of at least one

wetting agent. Col. 4, lines 39–44 the '791 patent (DX1).

21. Additionally, each of the Examples of the '791 patent specification exemplifies the preparation of the beads specifically describing mixing the bead components during the bead manufacturing stage, such as in a planetary mixer for approximately 15 minutes. Col. 5, lines 55–67 and col. 6, lines 4–15 of '791 patent (DX1).

22. The '791 patent issued as a continuation of two prior patent applications, one of which issued as a patent, and the other resulted in an abandonment. Cover of '791 patent (Def.Exh.1); '791 file history (Def.Exh.3); '505 file history (Def.Exh.4)

23. The original application was filed on June 26, 1991 and received Serial No. 721,396 ("the '396 application"). The '396 application eventually issued as United States Patent No. 5,288,505 on February 22, 1994 ("the '505 patent"). '505 file history (DX4).

24. The '505 patent has not been asserted against Andrx in the present lawsuit, and, in fact, is not listed in the FDA Orange Book as covering Tiazac®. Complaint; FDA Orange Book (DX12).

25. Prior to the issuance of the '505 patent, Biovail filed a continuation of the '396 application on May 28, 1993, which continuation application received Serial No. 68,951 ("the '951 application"). '791 patent file history (DX3).

26. The '951 application did not issue as a patent, but instead was abandoned in favor of another continuation application which was filed on September 23, 1994 and which received Serial No. 311,722 ("the '722 application"). 791 patent file history (DX3).

27. The '722 application eventually issued as the '791 patent on June 25, 1996.- '791 file history (DX3).

28. During the prosecution of the '951 application and the '396 application, Biovail consistently referred to the bead as comprising an admixture of the diltiazem and wetting agent during the manufacturing stage in order to avoid the prior art. '505 file history (DX4); '791 file history (DX3).

29. In fact, during the prosecution of the '951 application and the '396 application, Biovail made numerous representations to the USPTO that the claims required the diltiazem and wetting agent needed to be homogeneously admixed during the manufacturing state. '505 file history (DX4); '791 file history (DX3).

30. On pages 8–9 of the May 28, 1993 Preliminary Amendment in the '951 application, Biovail made the following representations regarding the scope of the claims to the USPTO:

> Thus, at the outset, it is noted that the present composition is characterized by the use of beads consisting essentially of *in admixture together* an effective amount of Diltiazem or one or more salts thereof as an active ingredient and the wetting agent as defined in the claims. The beads are also coated with a microporous membrane as defined in the claims.
>
> In essence, in admixture, the wetting agent appears to control, or strongly influence, the solubility of Diltiazem and does not permit this solubility to be affected by pH or other adverse conditions in the gastrointestinal tract. Further, this control appears to occur within the core of Diltiazem and wetting agent. This control affords a gradual release of Diltiazem in a relatively uniform manner over a period of about 24 hours. Further, the system of the present invention, as noted in the parent application is quite different from that of *Debregeas et al.* In particular, from column 3, lines 3–31 of *Debregeas et al*, it is clear that

the process thereof results in a compositional form having i) an 'core' of mutual excipients, which is described as a mixture of *saccharose or fructose and starch*, ii) an outer layer thereon of polyvinylpyrrolidone (PVP) and Diltiazem and iii) a coating thereon. Thus, in *Debregeas et al*, Diltiazem is in admixture *with only PVP*, and not with the "core of that composition."

By contrast, the present formulation contains Diltiazem or one or more salts thereof *in admixture together* with the wetting agent. By combining the wetting agent in admixture with Diltiazem or one or more salts thereof, the solubility of the Diltiazem may be controlled and rendered independent of pH. This is quite important due to the wide variation in pH in the gastrointestinal tract. (emphasis in original).

Pages 8–9 of May 28, 1993 Preliminary Amendment (Def.Exh.5).

31. The above-paragraph from the Preliminary Amendment was interpreted by Mr. Deboeck, one of the inventors of the '791 patent and the Rule 30(b)(6) designee of Biovail for the topic of the prosecution history of the '791 patent, as referring to a distinction which only exists at the time of manufacture of the products, i.e., in the dry state, and not after placement in an aqueous media. Page 75, line 16 to page 79, line 12 of Deboeck deposition transcript.

32. The prosecuting attorney for Biovail of the '791 patent testified in his deposition that he did not recall why he made the statement. Page 149, line 2 to page 15, line 5 of Beaumont deposition transcript.

33. On page 11 of the May 28, 1993 Preliminary Amendment in the '951 application, Biovail further represented to the USPTO that the admixing was dependent on the manufacturing process:

> ... in accordance with the present invention, the extrusion-spheronization process leads to *homogeneous* type beads while the "building-up" process, starting with a sugar core, leads to *heterogeneous* type beads. Clearly, it is impossible to have a sugar central core in a *homogeneous* bead as in the present invention. Such a bead is, by nature, *heterogeneous*. (emphasis in original).

Page 11 of May 28, 1993 Preliminary Amendment (DX5).

34. Additionally, on pages 13–14 of the May 28, 1993 Preliminary Amendment Biovail represented to the USPTO that a sucrose central core cannot constitute a wetting agent within the scope of the claims:

> ... The saccharose contained in the central core of the bead *cannot* act as a wetting agent because in order to do so the saccharose must be mixed with the Diltiazem and, therefore, saccharose must be in solution with Diltiazem. Unfortunately, in this system saccharose can only end up in solution after all the layers of Diltiazem are dissolved. In other words, saccharose can only become effective when there is not longer a need therefor. (emphasis in original).

Pages 13–14 of May 28, 1993 Preliminary Amendment (DX5).

35. Accordingly, the prosecution history of the '791 patent supports the interpretation that the claims of the '791 patent require the diltiazem and wetting agent to be in admixture at the time of manufacture and do not cover a formulation where the diltiazem is layered on top of a sugar sphere core. '791 file history (DX3); Banakar testimony.

## LITERAL INFRINGEMENT

36. The product for which Andrx has requested approval from the FDA to market as a bioequivalent form of Tiazac® is

the subject matter of ANDA 75–401 ("the Andrx product"). DX46.

37. The Andrx product does not include a wetting agent in admixture with diltiazem. Manufacture flow chart (DX43); Jan deposition testimony; CMC ANDA Section (DX46).

38. The Andrx product is comprised of beads which are placed in gelatin capsules. The beads themselves are comprised of three components, (i) an inert core, (ii) a drug layer, and (iii) a coating. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

39. The inert core of the Andrx product is comprised of spherical seeds which are referred to as sugar spheres and which are comprised of sucrose and starch. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

40. The drug layer of the Andrx product is comprised of a mixture of three components: (a) diltiazem HCl, (b) ethylcellulose (Ethocel 10cps) and (c) povidone (K–30). Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

41. The coating of Andrx product is comprised of five components: (1) Eudragit NE30D, (2) Hydroxypropyl Methylcellulose 2910 (Methocel E5), (3) magnesium stearate, (4) talc, and (5) polysorbate 80. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

42. A diagram of the Andrx product was shown wherein (a) represents the inert sugar sphere core, (b) represents the diltiazem containing layer, and (c) represents the coating. Non-infringement exhibit (DX38); Jan deposition testimony.

43. The manufacturing process for producing the Andrx product may be divided into six basic stages. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

44. In the first stage, Active Drug Layering, the diltiazem HCl is layered onto sugar spheres by suspension layering in a fluidized bed coater to produce active pellets which contain 75% diltiazem by weight. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

45. In the second stage, Extended Release Coating, the active pellets are then coated with a polymeric film in a fluidized bed coater to yield diltiazem HCl extended-release pellets. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

46. In the third stage, Blending, up to three sub-lots of diltiazem HCl extended-release pellets may be manufactured and blended to yield enough diltiazem HCl extended-release pellets for encapsulation of the maximum product batch size. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

47. In the fourth stage, Encapsulation, following testing and release, the diltiazem HCl extended-release pellets are filled into the appropriate size hard gelatin capsules. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

48. In the fifth stage, Check Weighing, during encapsulation, check weighing of the entire batch is performed if any individual capsule fill weight falls beyond ±8% of the target fill weight. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

49. In the sixth stage, Packaging and Labeling, following testing and release, the encapsulated product is packaged, as required, into to packaging sizes—30's and 1000's. Manufacture flow chart (DX43);

CMC ANDA section (DX46); Jan deposition testimony.

50. A flow chart of the manufacturing process is shown in Defendant's Exhibit 43. Manufacture flow chart (DX43); CMC ANDA section (DX46); Jan deposition testimony.

**COMPARISON OF ANDRX PRODUCT TO '791 PATENT CLAIMS**

51. The Andrx product avoids the literal claim language on a number of grounds. Banakar testimony; Weiner testimony.

52. The Andrx product does not contain a wetting agent in admixture with diltiazem as required by the claims of the '791 patent.

53. The term "admixture" means two or more items are commingled and interdispersed to obtain a homogeneous product.

54. The term "homogeneous" means that samples of the product taken anywhere throughout the product should have the same compositions.

55. The term "wetting agent" is defined as any of a group of surface active agents which, when added to a liquid, cause the liquid to spread more easily over, or penetrate into, a solid surface. Weiner testimony; Banakar testimony.

56. Ethylcellulose is not a wetting agent within the scope of the '791 patent claims. Biovail Response to Admission Request No. 8 (DX37).

57. Povidone (polyvinylpyrrolidone) is not a wetting agent within the scope of the '791 patent claims. Biovail Response to Admission Request No. 4 (DX37).

58. Neither polyvinylpyrrolidone or ethylcellulose are included in the list of wetting agents recited in claim 1 of the '791 patent. Col. 9, lines 5–13 of '791 patent (DX1); Biovail Response to Admission Request Nos. 6 and 7 (DX37).

59. At the time of manufacture, the diltiazem in the Andrx product is only in admixture with polyvinylpyrrolidone and ethylcellulose.

60. At the time of manufacture, the sugar sphere of the Andrx product cannot be considered to be in admixture with the diltiazem hydrochloride because in manufacturing the Andrx product the drug layer containing the diltiazem hydrochloride is layered onto the sugar sphere producing a heterogeneous or layered structure and not a homogeneous structure as required by the plain meaning of the term "admixture" in the claims of the '791 patent.

61. Sucrose is only a wetting agent when it is in the dry state.

62. Sucrose is not commonly referred to as a wetting agent because it is not surface active, i.e., it does not reduce the surface tension of water.

63. Instead sucrose is more commonly referred to as a dispersing or wicking agent, which may be classified as a wetting agent only because sucrose may have utility in helping to disperse solids in water. These types of wetting agents are solids which have no surface activity, but have very high water solubility.

64. When a solid has difficulty in wetting, it can be admixed with dispersing or wicking agents which easily wet, thereby increasing the permeability of water to the region of the solid which has difficulty in wetting, thus improving its ability to be dissolved by not allowing it to aggregate together to the extent that it would aggregate if these dispersing agents were not present.

65. For example, when one experiences problems adding an insoluble drug to a vat of liquid that needs to be dispersed in this vat, very often if they add the drug directly to the liquid it will "glomp up" and if

they try to stir it faster, the ball of "glomp" will just move faster. So a common technique for solving this problem is to take the drug with solid sugar, mix it intimately with the solid sugar and then add this admixture to the liquid, which improves the ability of the drug to be dispersed. Weiner testimony.

66. While solid sucrose may act as a dispersing or wicking agent, a sucrose solution acts as an anti-wetting agent. Weiner testimony; Banakar testimony.

67. Solid sucrose if it is interdispersed and intimately mixed with another solid will allow more water to come into contact with that solid because the solid sucrose is attracting the water. However, if sucrose is in solution, the water is already there, and in fact, sucrose and water mix extremely well. Thus, the water now has a choice of whether it will go to the solid or stay with the sucrose, it will always stay with the sucrose and go away from the solid because it is already very happy with its intimate mixture with sucrose. Weiner testimony.

68. There is no physical or chemical basis to support defining a hydrophilic or water-soluble non-surface active agent in water as a wetting agent, and because there is a disincentive for the hydrophilic or water-soluble non-surface active agent in water to act as wetting agent because the water is interacting more strongly with the hydrophilic or water-soluble non-surface active agent than with the solid surface you desire to wet, it is in fact more clearly defined as an anti-wetting agent. Weiner testimony.

69. Furthermore, all wetting agents decrease the surface tension of water. However, once sucrose has been dissolved in water the surface tension of water increases, thereby negating solid sucrose's tendency to wet a substance. Weiner testimony.

70. Biovail has failed to prove that an admixture between the sugar and the diltiazem forms in the body.

71. Biovail has admitted that as manufactured the Andrx product does not contain an admixture of diltiazem and wetting agent.

72. Andrx performs its dissolution testing in a USP Apparatus 2 (paddles) at 75 rpm. Biovail employed a shaker table at 30 rpm.

73. Biovail has provided no evidence that a shaker table provides equivalent results to what goes on in body. Conditions in gastrointestinal tract are not the same as those created in a shaker table.

74. Biovail's tests are not reliable for a number of reasons:

(a) no showing that beads used for weight loss study were equivalent (storage time, conditions, lot number, etc.) to those Andrx used in dissolution testing subtracted from weight loss to determine alleged sugar release,

(b) use of sodium azide (a strong ion that can affect dissolution and destroy the test),

(c) difference in shaker table v. dissolution apparatus,

(d) temperature control,

(e) effect of lyophilization,

(f) flow patterns or hydrodynamics will affect dissolution rate tests.

75. Biovail's own tests, particularly the Electron Scanning Microscope (ESM) slides submitted in evidence, do not show that a homogeneous admixture is formed in the Andrx product. Plaintiff's Exhibit 30 (Exhibit 30a et al.).

76. Biovail has not met its burden to show that the Andrx product employs an amount of a wetting agent which maintains the solubility of diltiazem in each bead.

77. In solution, sucrose does not function as a wetting agent and therefore no amount can be effective to maintain the solubility of diltiazem.

78. Biovail has not met its burden to show that the Andrx product employs an amount of a wetting agent which ensures that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

79. In solution, sucrose does not function as a wetting agent and therefore it cannot be effective to maintain the solubility of diltiazem.

## DOCTRINE OF EQUIVALENTS

### THE USE OF A SUGAR CORE IS A SUBSTANTIAL DIFFERENCE

80. Use of a solid sugar core as opposed to a sugar or another wetting agent in admixture with the diltiazem is a substantial difference.

81. The sugar core functions substantially differently because it is inert and does not function as a wetting agent.

82. The sugar core acts in a substantially different way because it does not provide any wetting to the diltiazem but merely provides a means for which to build up the diltiazem.

83. The sugar core provides a substantially different result because once solubilized it functions as an anti-wetting agent.

### SUCROSE STEARATE IS NOT EQUIVALENT TO SUCROSE

84. Regarding claim 4, sucrose stearate does not function in an equivalent manner to a solution of sucrose.

85. A solution of sucrose functions as an anti-wetting agent, while sucrose stearate functions as a wetting agent.

86. A sucrose core surrounded by a layer of diltiazem acts in a substantially different way from a mixture of diltiazem and sucrose stearate because it does not provide any wetting to the diltiazem.

87. Sucrose in solution does not form the same type of structure with diltiazem that sucrose stearate does.

## PRIOR ART ESTOPPEL

88. A product having a sugar sphere on top of which is built up a layer of diltiazem and polyvinylpyrrolidone having an outer coating thereon is within the prior art. '240 patent (DX7); '619 patent (DX8); '596 patent (DX9); '083 patent (DX10); '097 patent (DX11).

89. This was specifically admitted by Plaintiff in the prosecution history of the '791 patent. May 28, 1993 Preliminary Amendment (DX5).

90. Specifically, on page 9 of the May 28, 1993 Preliminary Amendment, Plaintiff stated as follows with regard to the Debregeas patent:

> In particular, from column 3, lines 3–31, of Debregeas et al, it is clear that the process thereof resulted in a compositional form having i)[a] 'core' of mutual excipient, which is described as a *mixture of saccharose or fructose and starch* [i.e. sugar], ii) an outer layer thereon of polyvinylpyrrolidone (PVP) and Diltiazem, and iii) a coating thereon. (emphasis in original) May 28, 1993 Preliminary Amendment (DX5).

91. This is an exact description of the composition of the Andrx formulation which is alleged to infringe the claims of the '791 patent (except that the Andrx formulation also contains ethyl cellulose in the layer built up on top of the sugar core). Jan deposition testimony; Banakar testimony.

92. Other prior art references also employ the same inert sugar core; diltiazem layer; coating structure which is employed by Andrx and taught in the '596 patent. For example, see, Panoz et al., United States Patent No. 4,721,619 ("the '619 patent"); Valducci, European Patent No. 0 263 083 ("the '083 patent"); Geogheghan et al., European Patent No. 0 320 097 ("the '097 patent"); Geogheghan et al., United States Patent No. 4,894,240 ("the '240 patent"); and the '596 patent. '240 patent (DX7); '619 patent (DX8); '596 patent (DX9); '083 patent (DX10); '097 patent (DX11); Banakar testimony.

93. To the extent any of these Findings of Fact constitute Conclusions of Law, they are hereby adopted as both.

## CONCLUSIONS OF LAW

1. The present action was brought by Plaintiffs (hereinafter "Biovail") for the alleged infringement of United States Patent No. 5,529,791 (hereinafter "the '791 patent") under 35 U.S.C. § 271(e)(2)(a) which defines a narrow act of infringement.

2. This narrow act of infringement derives from a statutory scheme which was enacted by Congress in the Drug Price and Patent Term Restoration Act, 98 Stat. 1585 (hereinafter "Patent Term Act"). The Patent Term Act sought to facilitate entry of lower priced bioequivalent drugs into the marketplace while also providing incentives for promoting the development of new drug products.

3. Accordingly, the Patent Term Act defined a new form of infringement, which was codified at 35 U.S.C. § 271(e)(2)(a), which covers the narrow situation wherein an ANDA is filed to obtain FDA approval for a drug product which is bioequivalent to a drug claimed in a patent listed in the FDA Orange Book, and which infringes the claims of the listed patent. 1984 U.S.C.C.A.N. 2678–79; 35 U.S.C. § 271(3)(2).

4. Upon the filing of an ANDA for a drug for which a patent is listed in the FDA Orange Book, the ANDA applicant is required to make one of four certifications regarding the patent. If the ANDA applicant makes what is known as a paragraph IV certification, i.e., that the ANDA applicant believes that the drug formulation described in the ANDA does not infringe the claims of the patent(s) listed in the FDA Orange Book, or that the claims of the listed patent are invalid, then the patent owner may file a lawsuit under 35 U.S.C. § 271(e)(2)(a) within forty-five days of the notice. 21 U.S.C. § 355(j)(5)(iii).

5. Upon the filing of such a lawsuit, the ANDA statute forbids the FDA from approving the ANDA until either there is a final decision of no infringement or invalidity by a United States court, or thirty months expires, whichever occurs first. 21 U.S.C. § 355(j)(5)(iii).

6. Plaintiffs filed the instant complaint on October 7, 1998, seeking: 1) a declaratory judgment that Defendant's submission of an ANDA for commercial production of its proposed generic equivalent of Tiazac® before the expiration of the '791 Patent constitutes infringement of the '791 patent; 2) an order under 35 U.S.C. § 271(e)(4)(A) directing the effective date of any approval of Defendant's proposed generic equivalent to be a date which is not earlier than the expiration of the '791 patent; 3) injunctive relief prohibiting Defendant from further infringing on the '791 patent; and 4) attorney fees and costs.

7. Defendant, in response, filed an answer and counterclaim seeking declaratory judgment and alleging the following claims: 1) Defendant has not infringed the '791 patent (Count I); 2) the '791 patent is invalid due to prior art, previous

full public disclosure of the alleged invention prior to the application for the '791 patent, and various other reasons for invalidity (Count II), 3) the '791 patent is invalid due to fraud by Plaintiff Galephar in submitting fees and a verified statement based upon Galephar's small entity status, when Galephar had already licensed its patent to a large entity (Count III); and 4) the '791 patent is invalid due to misuse by Plaintiffs in commencing "the present action in an unlawful attempt to impermissibly broaden the scope of the '791 patent with the anticompetitive effect of delaying and/or keeping the accused Andrx product from being marketed" (Count IV) (Count IV was previously dismissed by this Court).

***Claim Construction of the '791 Patent***

[1] 8. It is the Court's role to construe the claims of the disputed patent. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 116 S.Ct. 1384, 1387, 134 L.Ed.2d 577 (1996).

[2] 9. The Court principally looks to the claims made in the patent, the specifications, and the prosecution history. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed.Cir.1996).

[3] 10. Only if these are ambiguous, does the Court look to extrinsic evidence, such as expert affidavits or declarations. *Id.*

11. The claims herein appear specific enough to allow the Court to construe the claims without the need for extrinsic evidence for purposes of the motions for summary judgment.

12. Based on the '791 patent claim language, the specification of the '791 patent and the prosecution history which led to the issuance of the '791 patent, it is clear that the claims of the '791 patent require that the wetting agent and diltiazem be in admixture in the dry state. *Southwall Tech., Inc. v. Cardinal IG Co.*, 54 F.3d 1570 (Fed.Cir.1995).

**LITERAL INFRINGEMENT**

[4] 13. In order for a composition to literally infringe a claim, each and every element must be found in the accused product *exactly*. *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir.1995).

[5] 14. The burden to show literal infringement is on the patentee by a preponderance of evidence. *Braun Inc. v. Dynamics Corp.*, 975 F.2d 815 (Fed.Cir.1992).

[6] 15. In this case, Biovail has failed to meet its burden that Andrx's product infringed the '791 patent.

**DOCTRINE OF EQUIVALENTS**

[7] 16. The doctrine of equivalents is sometimes applied in patent cases to enable the claims of a patent to cover products not within the literal scope of the claim if the product only differs insubstantially from the claim language. *Hilton Davis Chem. Co. v. Warner Jenkinson Co.*, 62 F.3d 1512, 35 USPQ2d 1641 (Fed.Cir. 1996).

[8] 17. One way to show an insubstantial difference is to show that the substituted element provides substantially the same functions in substantially the same way to achieve substantially the same result. *Warner–Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997).

[9] 18. The burden to show infringement under the doctrine of equivalents is on the patentee by a preponderance of evidence. *Braun Inc. v. Dynamics Corp.*, 975 F.2d 815 (Fed.Cir.1992).

19. In reviewing the scientific evidence, the Court is mindful to follow the teachings of the Federal Circuit:

As we have repeatedly said, it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment of other version of the product or process; the only proper comparison is with the claims of the patent.

*Zenith Laboratories, Inc. v. Bristol–Myers Squibb*, 19 F.3d 1418, 1423 (Fed. Cir.1994); *Glaxo, Inc. v. TorPharm, Inc.*, 153 F.3d 1366, 1373 (Fed.Cir.1998).

20. In this case, Biovail has failed to prove infringement by Andrx's diltiazem product.

[10] 21. In making a doctrine of equivalents analysis, the scope of equivalents to which a claim may be allowed is limited by the doctrine of prosecution history estoppel. *Athletic Alternatives, Inc. v. Prince Mfg. Inc.*, 73 F.3d 1573, 1582 (Fed.Cir.1996).

[11] 22. Under the doctrine of prosecution history estoppel, actions taken by a patentee during the prosecution history act as legal limits on the application of the doctrine of equivalents by excluding from the range of equivalents subject matter surrendered during prosecution of the application for patent. The estoppel may arise from matter surrendered as a result of amendments to overcome patentability rejections, or as a result of argument to secure allowance of a claim. *Sextant Avionique S.A. v. Analog Devices, Inc.*, 172 F.3d 817, 49 USPQ2d 1865, 1870 (Fed.Cir. 1999).

[12] 23. A patentee is simply not entitled to greater rights under the doctrine of equivalents than he would be under the language of the claims of the patent. *White v. Dunbar*, 119 U.S. 47, 51–52, 7 S.Ct. 72, 74–75, 30 L.Ed. 303 (1886).

[13] 24. Unequivocal assertions or arguments made during the prosecution of a patent create an estoppel which bars application of the doctrine of equivalents. *Desper Prods. Inc. v. QSound Labs. Inc.*, 157 F.3d 1325, 48 USPQ2d 1088, 1098 (Fed. Cir.1998); *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1579 (Fed.Cir.1993).

[14] 25. A patentee who has limited claims of patents for controlled release drug formulation primarily in consideration of obviousness rejection, is estopped from asserting relinquished claim scope against a defendant under theory of infringement by equivalents. *Merck & Co. v. Mylan Pharms. Inc.*, 190 F.3d 1335, 51 USPQ2d 1954 (Fed.Cir.1999).

[15] 26. Statements made during the prosecution of a patent bar plaintiff from asserting the doctrine of equivalents infringement against accused products, regardless of whether the statements were required to distinguish prior art, where a reasonable competitor could conclude from the statements that the plaintiff disclaimed the subject matter at issue in order to obtain the issuance of the patent.

[16] 27. The Federal Circuit has stated that: "For an estoppel to apply, such assertions in favor of patentability must evince a clear and unmistakable surrender of subject matter." *Pharmacia & Upjohn Company v. Mylan Pharmaceuticals, Inc.*, 170 F.3d 1373, 1377 (Fed.Cir.1999) (internal quotation omitted).

[17] 28. The Court hereby concludes that Biovail did clearly and unmistakable surrender the building up process of using an inert sugar core in an extended release diltiazem product.

29. The Federal Circuit has also held that the relevant inquiry is whether a competitor would reasonably believe that the applicant had surrendered the relevant subject matter. *Cybor Corporation v. FAS Technologies, Inc.*, 138 F.3d 1448, 1457 (Fed.Cir.1998) (en banc).

30. In this case, a competitor would reasonable believe that Biovail had disclaimed the inert sugar core products in favor of their admixture form.

31. As an alternative conclusion to the above conclusion that Biovail has failed to meet its burden that Andrx infringed its patent, the Court concludes that because Biovail amended its claims to exclude a sugar core not in admixture with the diltiazem from the scope of the claims in response to a prior art rejection, Biovail is estopped from asserting that the inert sugar core of the Andrx formulation is a "wetting agent" within the scope of the claims of the '791 patent. *Ekchian v. Home Depot, Inc.*, 104 F.3d 1299, 1304 (Fed.Cir. 1997).

32. Such an amendment in response to a prior art rejection constitutes the essence of prosecution history estoppel and operates as a complete bar to infringement by doctrine of equivalents. *Sextant Avionique S.A. v. Analog Devices, Inc.*, 172 F.3d 817, 49 USPQ2d 1865, 1874–75 (Fed. Cir.1999).

33. Additionally, because Biovail continuously argued on numerous occasions that the use of a sugar core surrounded by a diltiazem layer to form a heterogeneous structure, as prepared by a "building up" process was not within the scope of the claims of the '791 patent, Biovail is estopped from asserting that the inert sugar core of the Andrx formulation is a "wetting agent" within the scope of the claims of the '791 patent. *Desper Prods. Inc. v. QSound Labs. Inc.*, 157 F.3d 1325, 48 USPQ2d 1088, 1098 (Fed.Cir.1998); *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1579 (Fed.Cir.1993).

34. It is only reasonable that explicit arguments made during the prosecution of a patent in order to overcome the prior art lead to a narrowing of the interpretation of the claims. As the Federal Circuit has held that "the public has a right to rely on such definitive statements made during prosecution." *Digital Biometrics v. Identix*, 149 F.3d 1335, 1347 (Fed.Cir.1998) (pointing to "[n]otice [as] an important feature of patent prosecution, as reflected by the [patent] statute itself").

35. The public's reliance on statements made during prosecution of a patent is entirely justified because "[b]y distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover." *Ekchian v. Home Depot, Inc.*, 104 F.3d 1299, 1304 (Fed.Cir. 1997).

## PRIOR ART ESTOPPEL

[18] 36. The doctrine of prior art estoppel provides a legal limitation on the application of the doctrine of equivalents by mandating that the asserted range of equivalents may not encompass the prior art at the very point at which the claims distinguish from that art.

[19] 37. The doctrine of prior art estoppel prevents the doctrine of equivalents from expanding the scope of the claims to protect subject matter in, or obvious in light of, the prior art. *Athletic Alternatives, Inc. v. Prince Mfg. Inc.*, 73 F.3d 1573, 1582 (Fed.Cir.1996).

38. Thus, because the Andrx formulation was admitted by Plaintiff to be within the scope of the prior art, the doctrine of equivalents cannot be asserted by Plaintiffs to bring the Andrx formulation within the scope of the '791 patent claims. *Stewart–Warner*, 767 F.2d at 1572; *Athletic Alternatives*, 73 F.3d at 1582.

39. The Court declines to reach the counterclaims for invalidity brought by Andrx against the Biovail patent given the Court's conclusions that Biovail has not proven that the Andrx product infringes the patent. Thus, resolution of the counterclaims is not necessary to provide

Andrx with the full relief it requested, namely, that its product does not infringe the Biovail patent

40. To the extent any of these Conclusions of Law constitute Findings of Fact, they are hereby adopted as both.

41. A separate Final Judgment will be entered herein consistent with the Court's Findings of Fact & Conclusions of Law.


**Yahweh Ben YAHWEH, Plaintiff,**

**v.**

**UNITED STATES PAROLE COMMISSION, Defendant.**

**No. 01–2848–CIV–MOORE.**

United States District Court, S.D. Florida, Miami Division.

Aug. 15, 2001.

Parolee sought declaratory judgment that conditions of his parole violated Religious Freedom Restoration Act (RFRA) and First Amendment, and moved for preliminary injunction against enforcement of conditions. The District Court, Moore, J., held that: (1) as matter of first impression, habeas corpus was not exclusive means to challenge parole conditions; (2) as matter of first impression, parolee was not required to exhaust administrative remedies; (3) conditions advanced compelling government interest; (4) conditions were reasonably related to legitimate purposes of parole; and (5) conditions did not violate parolees free association rights.

Motion denied.

**1. Declaratory Judgment ⇐41**

Habeas corpus was not exclusive remedy for parolee challenging conditions of parole as violative of RFRA, and thus, parolee could challenge conditions through declaratory judgment action; parolee's declaratory judgment action did not challenge fact or duration of confinement, and sought only prospective injunctive relief. Religious Freedom Restoration Act of 1993, § 2 et seq., 42 U.S.C.A. § 2000bb et seq.

**2. United States ⇐50.1**

Generally, courts apply § 1983 law to suits challenging constitutionality of actions of federal officials. 42 U.S.C.A. § 1983.

**3. Administrative Law and Procedure ⇐229**

To determine whether failure to exhaust federal administrative remedies precludes cause of action, court must determine: (1) whether operative statutes mandate exhaustion and, if so, that exhaustion is not discretionary with court, or (2) whether common law exhaustion requirement is applicable.

**4. Administrative Law and Procedure ⇐229**

Common-law requirement of exhaustion of administrative remedies should not be required where it may occasion undue prejudice to subsequent assertion of court action, where administrative remedy would be inadequate, or where administrative body has been shown to be biased or has otherwise predetermined issue before it.

**5. Declaratory Judgment ⇐41**

There was no common-law requirement that parolee seeking declaratory judgment that parole conditions violated RFRA had to exhaust administrative remedies first; action challenged procedures employed by parole commission in setting

# EXHIBIT B

COSTS

Each party shall bear its own costs.


**BIOVAIL CORPORATION INTERNATIONAL, Biovail Laboratories, Inc., and Galephar P.R., Inc., Ltd., Plaintiffs–Appellants,**

**v.**

**ANDRX PHARMACEUTICALS, INC., Defendant–Appellee.**

**No. 00–1260.**

United States Court of Appeals, Federal Circuit.

Decided Feb. 13, 2001.

Licensees of patent for hypertension drug sued generic drug manufacturer for infringement. The United States District Court for the Southern District of Florida, William P. Dimitrouleas, J., determined that patent was not infringed, and licensees appealed. The Court of Appeals, Gajarsa, Circuit Judge, held that: (1) admixture of diltiazem salt and wetting agent that comprised bead of patent claim was homogeneous; (2) district court's determination that defendant's product did not literally infringe plaintiff's patent was not clearly erroneous; and (3) defendant's product did not infringe plaintiff's patent under doctrine of equivalents.

Affirmed.

**1. Patents ⇐324.5**

Patent claim construction is matter of law that Court of Appeals reviews de novo.

**2. Patents ⇐324.55(5)**

Literal infringement of patent is question of fact that Court of Appeals reviews under clearly erroneous standard.

**3. Patents ⇐324.5**

Prosecution history estoppel is legal question subject to de novo review by Court of Appeals.

**4. Patents ⇐324.55(5)**

Infringement under doctrine of equivalents is factual finding reviewed by Court of Appeals for clear error.

**5. Patents ⇐165(1), 167(1), 168(2.1)**

To construe patent claim, court first analyzes intrinsic evidence of record, the claims and written description of patent itself, and, if in evidence, the prosecution history.

**6. Patents ⇐159**

When intrinsic evidence unambiguously describes scope of patented invention, reliance on extrinsic evidence is improper.

**7. Patents ⇐162**

Although words in patent claim are generally given their ordinary and customary meaning, patentee may choose to be his own lexicographer and use terms in manner other than their ordinary meaning, as long as special definition is clearly stated in patent specification or file history.

**8. Patents ⇐167(1), 168(2.1)**

Court reviews both specification and applicable prosecution history of patent to determine whether patentee defined claim terminology in manner inconsistent with its ordinary meaning.

**9. Patents ⇐101(3)**

Generally, limitation that does not exist in patent claim should not be read into that claim.

**10. Patents ⇐101(3)**

Although neither claims nor specification of drug patent required that "admixture" of diltiazem salt and wetting agent contained in beads be homogeneous, prosecution history of another patent derived from same initial application indicated that "bead" described was homogenous.

**11. Patents ⇐168(2.1)**

Patent claim language must be read consistently with totality of patent's applicable prosecution history.

**12. Patents ⇐168(2.1)**

When multiple patents derive from same initial application, prosecution history regarding claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain same claim limitation.

**13. Patents ⇐226.6, 312(4)**

Literal infringement requires patentee to prove by preponderance of the evidence that every limitation of asserted claim is literally met by allegedly infringing device.

**14. Federal Courts ⇐848**

Trial judge or jury who hears witnesses and initially assesses evidence deserves considerable latitude in making findings of fact, particularly scientific findings of fact.

**15. Patents ⇐250**

District court's determination that "sugar" in defendant's drug did not form homogeneous admixture with diltiazem in the body and thus did not literally infringe claim of patent requiring homogenous admixture was not clearly erroneous.

**16. Patents ⇐168(2.1), 237, 251**

When claim amendment creates prosecution history estoppel with regard to claim element, there is no range of equivalents available for amended claim element, that is, application of doctrine of equivalents to that claim element is completely barred; this complete bar applies regardless of whether amendment is explained or unexplained, if amendment narrows scope of claim for reason related to patentability.

**17. Patents ⇐168(3)**

Because "admixture" limitation was added to patent claim language in the prosecution history for reasons related to patentability, patent licensees were barred from claiming that any product not containing "admixture," as construed to be homogenous, infringed patent claim for hypertension drug under doctrine of equivalents.

**18. Patents ⇐292.3(2)**

Even after close of discovery in licensees' patent infringement action against generic drug manufacturer, manufacturer was required to disclose to licensees amendments to its Abbreviated New Drug Application (ANDA) for generic version of the drug. Federal Food, Drug, and Cosmetic Act, § 505(j)(2)(A)(vii)(IV), (j)(2)(B), 21 U.S.C.A. § 355(j)(2)(A)(vii)(IV), (j)(2)(B); 21 C.F.R. § 314.95.

---

Eric C. Cohen, Welsh & Katz, Ltd., of Chicago, IL, argued for plaintiffs-appellants. With him on the brief were A. Sidney Katz, Robert B. Breisblatt, Philip D. Segrest, Jr., and Charles R. Krikorian. Of counsel was Benedict P. Kuehne, Sale & Keuhne, P.A., of Miami, Florida.

James V. Costigan, Hedman, Gibson & Costigan, P.C., of New York, NY, argued for defendant-appellee. With him on the brief were Martin P. Endres, and Alan B. Clement. Of counsel on the brief was Gerald J. Houlihan, Houlihan & Partners, P.A., of Miami, Florida.

Before NEWMAN, CLEVENGER, and GAJARSA, Circuit Judges.

## DECISION

GAJARSA, Circuit Judge.

Biovail Corporation International, Biovail Laboratories, Inc., and Galephar P.R., Inc., Ltd. (collectively "Biovail") appeal the decision of the United States District Court for the Southern District of Florida, *Biovail Corp. Int'l v. Andrx Pharm., Inc.*, No. 98–CV–7096 (S.D.Fla. Mar. 6, 2000), which determined after a bench trial that Andrx Pharmaceuticals, Inc. ("Andrx") does not infringe United States Patent No. 5,529,791 ("the '791 patent") either literally or under the doctrine of equivalents. We affirm.

## BACKGROUND

Biovail Corporation International and Biovail Laboratories, Inc. are the exclusive licensees of the '791 patent, which is owned by Galephar P.R., Inc., Ltd. The '791 patent is directed to a once-a-day drug used to treat hypertension and angina. Claim 1 is the only independent claim of the '791 patent and is the only claim at issue in this case. It reads:

> 1. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises
>
> beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient,
>
> *each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead,* ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein,
>
> said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid-, and base-insoluble polymer and a pharmaceutically-acceptable adjuvant, and
>
> *wherein the wetting agent is selected from the group consisting of sugars,* $C_{12}$ $-C_{20}$ fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, esters of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

U.S. Patent No. 5,529,791 (issued June 25, 1996) (emphasis and paragraphing added). Biovail markets the drug described in the '791 patent under the trade name Tiazac.

On June 22, 1998, Andrx filed an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FD & C Act") for a generic version of Tiazac®. *See* 21 U.S.C. § 355(j) (1994). Andrx also filed a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), asserting that its ANDA product does not infringe the '791 patent and that the '791 patent is invalid.

Andrx's product comprises a bead encapsulated by a microporous membrane. This bead contains both diltiazem hydrochloride (a diltiazem salt) and sugar. Unlike Biovail's product, in Andrx's beads these components are not mixed during the manufacturing process. Rather, as produced, Andrx's bead is comprised of a sugar/starch core surrounded by a mixture of diltiazem hydrochloride, ethylcellulose, and polyvinylpyrrolidone.

On October 7, 1998, Biovail filed an action in the United States District Court for the Southern District of Florida alleging patent infringement pursuant to 35 U.S.C. § 271(e)(2)(A), which provides that it is an act of infringement to submit an applica-

tion under section 505(j) of the FD & C Act for a drug claimed in a patent. Andrx denied infringing the '791 patent and counterclaimed that the '791 patent is invalid. The district court denied cross-motions for summary judgment. It subsequently held a bench trial, conducting both claim construction and infringement analyses.

The court construed the term "admixture" in claim 1 of the '791 patent to describe "two or more items [that] are commingled and interdispersed to obtain a homogeneous product." Citing expert testimony, it construed the term "wetting agent" as "any of a group of surface active agents which, when added to a liquid, cause the liquid to spread more easily over, or penetrate into, a solid surface."

The court proceeded to make several findings of fact. It determined that: "Biovail has failed to prove that an admixture between the sugar and the diltiazem [in Andrx product] forms in the body." The court found Biovail's tests unreliable and further stated: "Biovail's own tests ... do not show that a homogeneous admixture is formed in the Andrx product."

Based on its factual findings and claim construction, the district court determined that Andrx's product did not literally infringe the '791 patent. It also found that Biovail amended its claims during prosecution to "exclude a sugar core not in admixture with the diltiazem ... in response to a prior art rejection." Therefore, the district court concluded that "Biovail is estopped from asserting that the inert sugar core of the Andrx formulation is a 'wetting agent' within the scope of the claims of the '791 patent" and consequently held that such prosecution history estoppel "operates as a complete bar to infringement by [the] doctrine of equivalents."

## DISCUSSION

### A. Standard of Review

[1–4] Claim construction is a matter of law that this court reviews *de novo*. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979, 34 USPQ2d 1321, 1329 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Literal infringement is a question of fact that we review under the clearly erroneous standard. *Amhil Enters. Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1562, 38 USPQ2d 1471, 1476 (Fed.Cir.1996). "A finding is 'clearly erroneous' when although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *Id.* at 1562, 38 USPQ2d at 1476 (quoting *United States v. United States Gypsum Co.*, 333 U.S. 364, 395, 68 S.Ct. 525, 92 L.Ed. 746 (1948)). Prosecution history estoppel is a legal question subject to *de novo* review on appeal to this court. *Cybor Corp. v. FAS Techs. Inc.*, 138 F.3d 1448, 1460, 46 USPQ2d 1169, 1178 (Fed.Cir.1998) (en banc). Infringement under the doctrine of equivalents is a factual finding reviewed for clear error. *Ryco, Inc. v. Ag–Bag Corp.*, 857 F.2d 1418, 1426, 8 USPQ2d 1323, 1329 (Fed.Cir.1988).

### B. Claim Construction

[5, 6] To construe a patent claim, a court first analyzes the intrinsic evidence of record—the claims and written description of the patent itself, and, if in evidence, the prosecution history. *Markman*, 52 F.3d at 979, 34 USPQ2d at 1329. When intrinsic evidence unambiguously describes the scope of a patented invention, reliance on extrinsic evidence is improper. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1577 (Fed. Cir.1996).

[7, 8] "Although words in a claim are generally given their ordinary and customary meaning, a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition is clearly

stated in the patent specification or file history." *Id.* at 1582, 39 USPQ2d at 1576. Therefore, we review both the specification and the applicable prosecution history to determine whether the patentee defined claim terminology in a manner inconsistent with its ordinary meaning. *Id.* at 1582, 39 USPQ2d at 1577.

It is not necessary for this court to construe the term "wetting agent." That is, the outcome of this case does not hinge on whether the sugar used in the core of Andrx's product meets the "wetting agent" limitation of claim 1 of the '791 patent.[1] This court also need not determine whether claim 1 of the '791 patent is limited to the product in its dry state or extends to the form of the product *in vivo*, because the outcome of this case does not turn on that issue.

[9–11] This case turns on whether the "admixture" limitation in claim 1 of the '791 patent must be "homogeneous." As a general proposition, a limitation that does not exist in a claim should not be read into that claim. *See McCarty v. Lehigh Valley R. Co.*, 160 U.S. 110, 116, 16 S.Ct. 240, 40 L.Ed. 358 (1895). Neither the claims nor the specification of the '791 patent require the "admixture" to be "homogeneous." Claim language, however, must be read consistently with the totality of the patent's applicable prosecution history. *Vitronics*, 90 F.3d at 1582, 39 USPQ2d at 1577; *Elkay Mfg. Co. v. EBCO Mfg. Co.*, 192 F.3d 973, 978, 52 USPQ2d 1109, 1112–13 (Fed.Cir.1999).

The '791 patent results from a series of continuation applications stemming from Application No. 721,396 ("the '396 application"), which was filed on June 26, 1991. After multiple amendments, certain claims of the '396 application issued as claims in United States Patent No. 5,288,505 ("the '505 patent") on February 22, 1994. Biovail also filed a continuation of the '396 application on May 28, 1993—Application No. 68,951 ("the '951 application"). After the '951 application was rejected for, *inter alia*, double patenting over the '505 patent, Biovail abandoned the '951 application in favor of another continuation—Application No. 311,722 ("the '722 application"). The '722 application eventually issued as the '791 patent on June 25, 1996.

[12] "When multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation." *Elkay*, 192 F.3d at 980, 52 USPQ2d at 1114; *see also Jonsson v. The Stanley Works*, 903 F.2d 812, 817–18, 14 USPQ2d 1863, 1868 (Fed.Cir.1990) (providing that when two patents issued from continuation-in-part applications derived from one original application, the prosecution history of a claim limitation in the first patent to issue was properly applied to the same limitation in the second patent to issue). The claims in the '396 application as originally filed did not include the term "admixture." The "admixture" limitation was added to claims in the '396 application following an amendment after final rejection, and these claims issued as claims in the '505 patent. The '505 and '791 patents both derive from the initial '396 application. The "admixture" limitation appears in a similar context in both the '505 and '791 patents. Therefore, any prosecution history relating to the "admixture" limitation of the '505 patent (which includes the prosecution history of the '396 application) applies with equal force to that limitation in claim 1 of the '791 patent.

The initial '396 application was first rejected, *inter alia*, as anticipated by United

1. If intrinsic evidence, including the Markush group in claim 1 and the list of wetting agents in the specification of the '791 patent unambiguously define the term "wetting agent," then the district court's reliance on expert testimony to construe this term was improper.

States Patent No. 4,960,596, which issued to Debregeas et al. (the "Debregeas patent").[2] After an amendment, the '396 application was finally rejected, *inter alia*, in view of Debregeas. Subsequent to an interview with the examiner, the '396 applicant added the "admixture" limitation to the relevant claims in an amendment after final rejection.[3]

To distinguish Debregeas in the remarks accompanying this amendment, the applicant stated: "By contrast [to the Debregeas invention,] the extrusion-spheronization process [of the invention in the '396 application] leads to *homogeneous* type beads while the 'building-up' process [of the Debregeas invention], starting with a sugar core, leads to *heterogeneous* type beads." (emphasis in original). The applicant further argued: "Clearly, it is impossible to have a sugar central core in a *homogeneous* bead as in [the '396 application]. Such a bead [with a sugar central core] is, by nature, *heterogeneous*." (emphasis in original). The remarks accompanying the amendment after final rejection also provided that a bead produced by the extrusion-spheronization process of the '791 patent "is necessarily a *homogeneous* bead composition." (emphasis in original).

The '396 applicant also discussed Debregeas with the examiner in an interview after the final rejection of the '396 application, but prior to the applicant's submission of the amendment after final rejection. The examiner summary of that interview provides: "A declaration will be submitted.... A showing of a homogeneous admixture of [d]iltiazem in combination with the wetting agent[ ] ... would be considered for distinction over [Debregeas]." The inventor of the product described in the '396 application subsequently submitted a declaration. In the remarks accompanying the amendment after final rejection the applicant discussed that declaration, arguing, "the [d]eclaration establishes that the 'core' or 'center' of the present composition is homogeneous with respect to diltiazem and wetting agent." Further, the experiment discussed in the declaration provides, "that the 'center' or 'core' [of the product in the '396 application] is an inherently homogeneous or uniform composition of diltiazem of one or more salts and wetting agent...." After submission of the declaration and the amendment after final rejection—which added the "admixture" limitation—the examiner allowed the relevant claims over Debregeas. These claims issued as claims 1, 6, and 11 of the '505 patent.

The prosecution history of the '396 application clearly indicates that at least the "bead" described in the '396 application, in claims 1, 6, and 11 of the '505 patent, and in claim 1 of the '791 patent must be "homogeneous." Claim 1 of the '791 patent provides that the "bead" contains a diltiazem salt and a wetting agent in "admixture." Therefore, the admixture of diltiazem salt and wetting agent that comprises the bead of claim 1 of the '791 patent must be homogeneous.

### C. Literal Infringement

[13] Literal infringement requires a patentee to prove by a preponderance of the evidence that every limitation of the asserted claim is literally met by the allegedly infringing device. *Enercon v. Int'l Trade Comm'n*, 151 F.3d 1376, 1384, 47 USPQ2d 1725, 1731 (Fed.Cir.1998).

2. The Debregeas patent discloses a bead containing a sugar/starch core surrounded by diltiazem, which is encapsulated by an outer membrane containing shellac.

3. For example, this amendment changed a limitation providing, "beads comprising an effective amount of one or more [d]iltiazem salts ... and a wetting agent" to one requiring "beads consisting essentially of in admixture together an effective amount of [diltiazem] or one or more salts thereof ... and an effective amount of wetting agent."

Biovail does not contend that Andrx's product is homogeneously admixed in the dry state. The district court assessed a multitude of evidence, including expert witness testimony, to determine whether a homogeneous admixture of Andrx's product forms *in vivo*.

The district court stated in its factual findings that "Biovail's tests are not reliable," listed several reasons for this determination, and concluded: "Biovail's own tests, particularly the Electron Scanning Microscope ("ESM") slides submitted in evidence, do not show that a homogeneous admixture is formed in the Andrx product." It also determined as a finding of fact that, "Biovail has failed to prove that an admixture between the sugar and the diltiazem [in Andrx's product] forms in the body." The district court had previously construed "admixture" as "two or more items ... commingled and interdispersed to obtain a homogeneous product." Therefore, the district court construed "admixture" in a manner consistent with this court's construction of that limitation. Consequently, when the district court found that Biovail failed to prove Andrx's product formed an admixture in the body, it referred to a homogeneous admixture.

[14, 15] Appellate courts are not ideally suited to unravel the processes of scientific phenomena. *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423, 30 USPQ2d 1285, 1289 (Fed.Cir. 1994). A trial judge or jury who hears witnesses and initially assesses evidence deserves considerable latitude in making findings of fact, particularly scientific findings of fact. *Id.* Indeed, the Supreme Court has charged trial court judges with the responsibility of performing a gatekeeping function to ensure that all expert testimony, including scientific testimony, is not only relevant, but also reliable. *See Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 147, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999) (extending the basic gate-keeping obligation for "scientific" testimony established in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 589, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993), to all expert testimony). The district court in this case analyzed a significant amount of scientific evidence and made factual findings based on that evidence. Regardless of its construction of the limitation "wetting agent," the district court found Biovail failed to prove by a preponderance of evidence that the "sugar" in Andrx's product forms a homogeneous admixture with diltiazem in the body. Because this finding was clearly supported by the evidence, it does not leave this court with "a definite and firm conviction that a mistake has been committed." Therefore, even assuming *arguendo* that "admixture" is not limited to dry state compositions and that sugar as used in Andrx's product is a "wetting agent," the district court's determination that Andrx's product does not literally infringe claim 1 of the '791 patent was not clearly erroneous.

### D. Prosecution History Estoppel/Doctrine of Equivalents

[16] This case falls squarely within the reach of this court's decision in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir.2000) (en banc). "When a claim amendment creates prosecution history estoppel with regard to a claim element, there is no range of equivalents available for the amended claim element." *Id.* at 569, 56 USPQ2d at 1872. That is, "[a]pplication of the doctrine of equivalents to [that] claim element is completely barred...." *Id.* This complete bar applies "regardless of whether the amendment is explained or unexplained, if the amendment narrows the scope of the claim for a reason related to patentability...." *Id.* at 576, 56 USPQ2d at 1878.

[17] In this case, the '391 applicant added the term "admixture" to the pertinent claims in the amendment after final rejection of the '396 application—prosecution history that applies to the "admixture" limitation of claim 1 of the '791 patent—to distinguish Debregeas. This amendment was related to patentability. Indeed, the '505 patent issued with the "admixture" limitation shortly after it was added. Further, in the examiner's summary of an interview with the applicant prior to submission of the amendment after final rejection of the '396 application, the examiner stated that a declaration, which was subsequently submitted, "showing ... a homogeneous admixture of [d]iltiazem in combination with the wetting agent ... would be considered for distinction over [Debregeas]."

Because the "admixture" limitation was added to the pertinent claim language in the relevant prosecution history for reasons related to patentability, Biovail is completely barred from claiming that any product not containing an "admixture" as properly construed by this court infringes claim 1 of the '791 patent under the doctrine of equivalents. *Id.* That is, when application of the doctrine of equivalents to a limitation is completely barred due to prosecution history estoppel, a patentee asserting infringement must show by a preponderance of the evidence that an allegedly infringing device literally reads on that limitation as properly construed.

We have determined that the "admixture" limitation in claim 1 of the '791 patent must be homogeneous. Biovail does not contend that diltiazem salt and sugar in Andrx's product are homogeneously admixed in the dry state. As discussed previously, the district court's factual findings that Biovail failed to prove by a preponderance of evidence that Andrx's product forms a homogeneous admixture in the body are not clearly erroneous. Therefore, Andrx's product does not meet the "admixture" limitation of claim 1 of the '791 patent either in the dry state or *in vivo*. Consequently, based on the complete bar raised by prosecution history estoppel, Andrx's product does not infringe claim 1 of the '791 patent under the doctrine of equivalents.

### E. Biovail's Motion for Vacatur and Remand

[18] Biovail has moved for vacatur and remand on the ground that Andrx did not advise Biovail of several (eleven) amendments filed to the ANDA after the close of discovery, and which were not made known to Biovail until after trial and decision and only shortly before scheduled appellate argument. It is an abuse of the judicial role for Andrx to ask us to review on appeal what should have been made known, and adequately explored, at trial. Under 21 U.S.C. § 355(j)(2)(B), there is an obligation to disclose the filing of an ANDA, as well as its content, to the patent holder and other interested parties. *See* 21 C.F.R. § 314.95 (2000). The obligation to inform the parties, and the trial court, as to any material amendment to the ANDA continues throughout the litigation that is artificially provoked under Paragraph IV. Andrx's failure to disclose the amendments it filed to the ANDA after the close of discovery constitutes a violation of that obligation.

However, in the interest of bringing this case to closure, we have reviewed the texts of these amendments, which have been provided in response to the motion now before us. We conclude that the amendments do not show reversible error in the district court's decision that infringement does not lie.

### F. Attorneys' Fees

Andrx filed a motion seeking attorneys' fees. This motion is denied.

## CONCLUSION

For the reasons set forth in this opinion, we affirm the district court's judgment

that Andrx's product neither literally infringes claim 1 of the '791 patent nor infringes that claim under the doctrine of equivalents.

*AFFIRMED.*

COSTS

Each party shall bear its own costs.


**FOREST LABORATORIES, INC. and ONY Inc., Plaintiffs–Cross Appellants,**

**v.**

**ABBOTT LABORATORIES, Defendant–Appellant**

**and**

**Tokyo Tanabe Co., Ltd., (acquired by Mitsubishi–Tokyo Pharmaceuticals, Inc.), Defendant–Appellant.**

**Nos. 99–1494, 99–1495 and 99–1512.**

United States Court of Appeals, Federal Circuit.

Decided Feb. 13, 2001.

Developers of lung surfactant composition for treating respiratory distress syndrome (RDS) in premature babies brought suit against assignee and licensee of patent for competing product, seeking declaratory judgment of non-infringement and patent invalidity. Defendants counterclaimed for infringement. Following jury verdict of infringement, the United States District Court for the Western District of New York, Richard J. Arcara, J., granted defendants' motion for judgment as a matter of law. Plaintiffs appealed. The Court of Appeals, Lourie, Circuit Judge, held that: (1) patent claim covered all surface active material that met claim limitations, regardless of its form as pre- or post-suspension material; (2) expression "based on dry weight" meant based on dry weight of surface active material before it was combined with carrier to form pharmaceutical composition; (3) there was no proof that accused product, based on its dry weight, possessed percentage of water claimed by the patents.

Affirmed.

**1. Federal Courts ⇐776**

Court of Appeals review district court's decision granting motion for judgment as a matter of law (JMOL) de novo, reapplying the JMOL standard.

**2. Federal Courts ⇐801, 844, 845**

On appeal of judgment as a matter of law (JMOL), Court of Appeals must consider record evidence in light most favorable to non-movant and draw all reasonable inferences in its favor without disturbing jury's credibility determinations or substituting Court's resolutions of conflicting evidence for those of jury.

**3. Federal Courts ⇐765**

Court of Appeals will affirm grant of judgment as a matter of law (JMOL) if substantial evidence does not support jury's factual findings or if those factual findings do not support jury's legal conclusions.

**4. Patents ⇐165(1), 167(1), 168(2.1)**

In interpreting patent claims, court should look first to intrinsic evidence of

# EXHIBIT C

US005529791A

# United States Patent [19]

Deboeck et al.

[11] Patent Number: 5,529,791

[45] Date of Patent: Jun. 25, 1996

[54] **EXTENDED RELEASE FORM OF DILTIAZEM**

[75] Inventors: **Arthur M. Deboeck**, Gurabo, Puerto Rico; **Philippe R. Baudier**, Waterloo, Belgium

[73] Assignee: **Galephar P.R., Inc., Ltd.**, Carolina, Puerto Rico

[21] Appl. No.: **311,722**

[22] Filed: **Sep. 23, 1994**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 68,951, May 28, 1993, abandoned, which is a continuation of Ser. No. 721,396, Jun. 26, 1991, Pat. No. 5,288,505.

[51] **Int. Cl.**[6] ..... **A61K 9/16**; A61K 9/58; A61K 9/62

[52] **U.S. Cl.** ..... **424/494**; 424/490; 424/497; 514/777; 514/785; 514/786; 514/970

[58] **Field of Search** ..... 424/457, 458, 424/462, 490, 493, 497, 498, 499, 494

[56] **References Cited**

U.S. PATENT DOCUMENTS

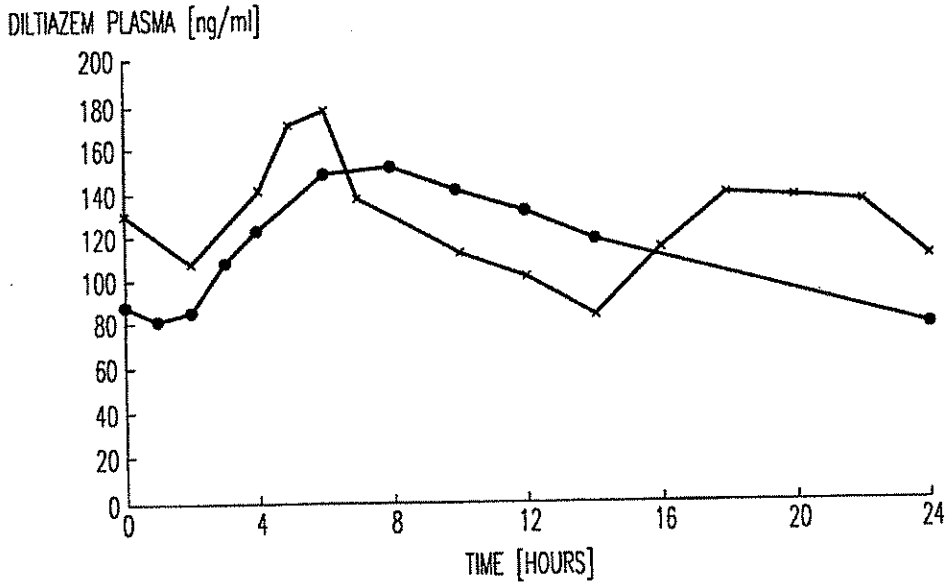
| | | | |
|---|---|---|---|
| 5,112,621 | 5/1992 | Stevens et al. | 424/497 |
| 5,275,824 | 1/1994 | Carli et al. | 424/490 |

*Primary Examiner*—Thurman K. Page
*Assistant Examiner*—James M. Spear
*Attorney, Agent, or Firm*—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

**4 Claims, 2 Drawing Sheets**



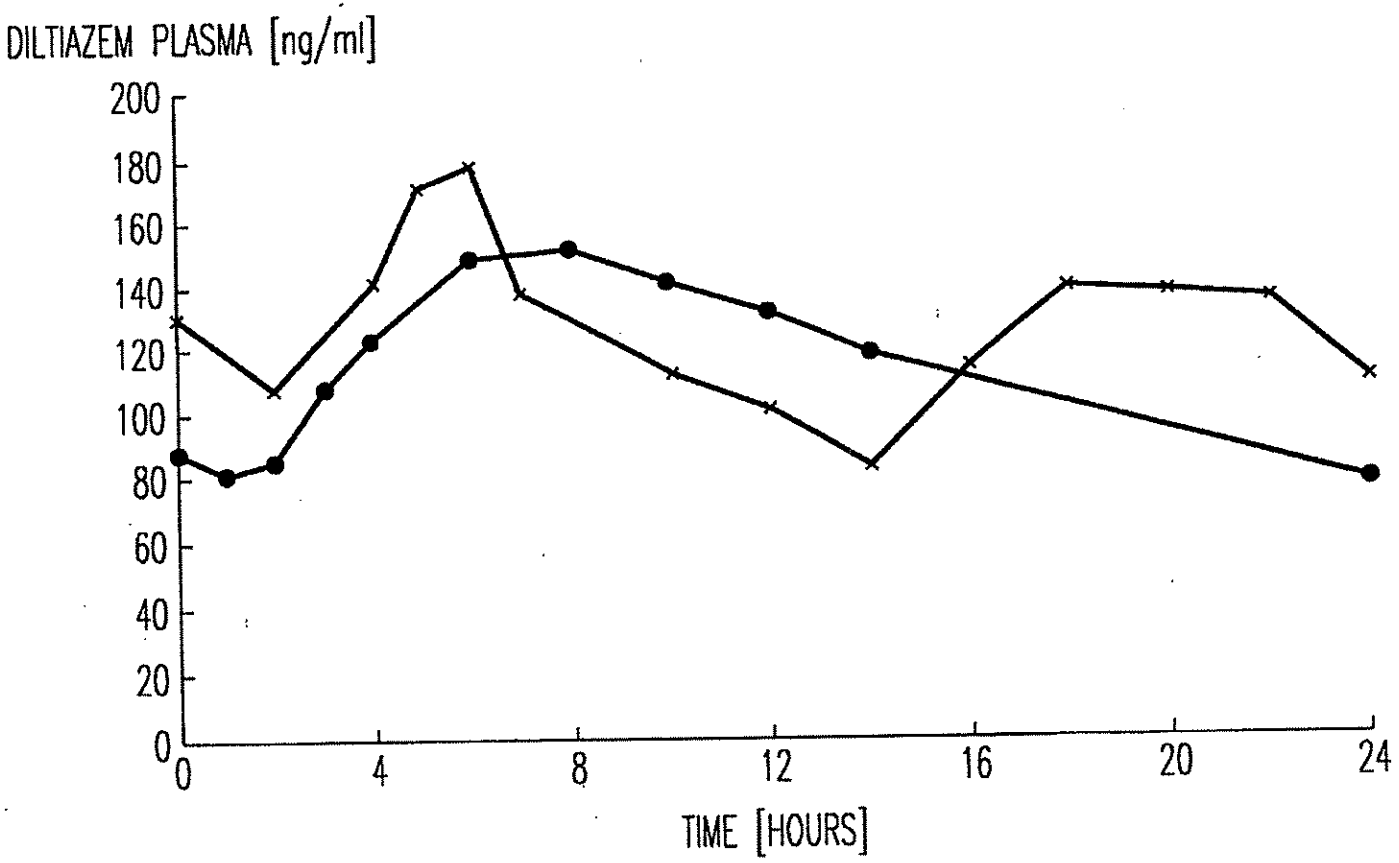

DILTIAZEM PLASMA [ng/ml]
200
180
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
TIME [HOURS]

*FIG. 1*

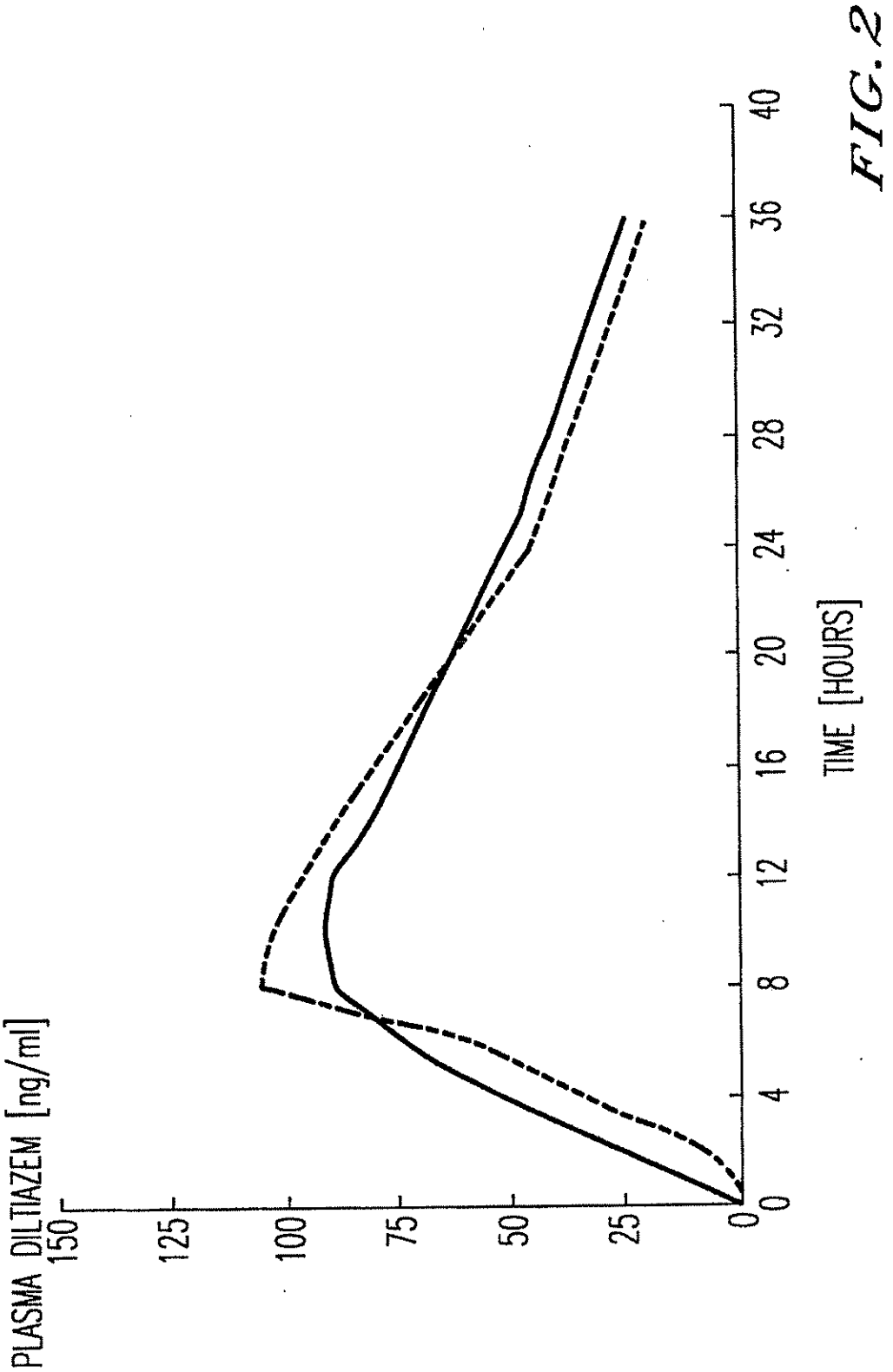

PLASMA DILTIAZEM [ng/ml]
150
125
100
75
50
25
0
0
4
8
12
16
20
24
28
32
36
40
TIME [HOURS]

FIG. 2

# EXTENDED RELEASE FORM OF DILTIAZEM

This application is a continuation of application Ser. No. 08/068,951, filed on May 28, 1993, now abandoned, which is a continuation of application Ser. No. 07/721,396 filed Jun. 26, 1991, now U.S. Pat. No. 5,288,505.

## BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

2. Description of the Background

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension; either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in human is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-released of Diltiazem known under the trade name CARDIZEM SR® was developed and presented in the form of "erodible pellets", U.S. Pat. No. 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. Pat. No. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and methylene chloride which are dangerous to use due to their flammability and toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.



Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food, and, further, which can be made by a process not using organic solvents.

## SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

FIG. 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2,(4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more than 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. Pat. No. 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they

may also include the acetate, citrate or lactate salts, for example. It is preferred however, that the hydrochloride salt be used.

In more detail, the microporous membrane whereof the Diltiazem containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer and including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

saccharose, mannitol, sorbitol;

lecithins;

polyvinylpyrrolidones;

$C_{12}$ to $C_{20}$ fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above named wetting agents the beads may contain excipients or carriers, such as: Microcrystalline celluloses, such as Avicel products (FMC, U.S.A); methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.); and starches.

Among the water-soluble and/or dispersible film forming polymers or copolymers constituting the microporous membrane, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS-30 D of Röhm Pharma (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropylmethylcellulose and their derivations.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

plastifying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;

pigments, such as iron oxides and titanium oxide;

fillers, such as lactose and sucrose;

wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;

lubricants, such as magnesium stearate and talc;

antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

The weight of the microporous membrane may be 2 to 35%, preferably, 5 to 22%, of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tractus, said process entailing preparing beads and coating the same with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder of ALEXANDER WERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJIU-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pilling turbine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known planetary granulator such as the collette (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of anyone of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

20 to 85%; Diltiazem hydrochloride

2 to 20% sucroesters WE 15 (wetting agent);

5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);

2 to 10% Methocel E 5 (hydroxypropylmethylcelulose of DOW, U.S.A.);

1 to 15% polyvinylpyrrolidone and

5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pul-

verization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient, however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only example and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example.

As examples of duretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired, however, they need not be.

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

According an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting form an aqueous dispersion which contains by weight:

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plastifying agent)
0.01 to 2% silicone oil (antifoaming agent);
0.05 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

## EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended release galenic forms, a process for preparing the same, therapeutic applications therefor and pharmacokinetic controls using the present galenic forms.

### Example 1—beads manufacture

| | |
|---|---|
| Diltiazem hydrochloride | 1120 g |
| Lactose | 119 g |
| Microcrystalline cellulose (Avicel pH 101) | 140 g |
| Povidone k 30 | 21 g |

After introducing the powders into a planetary mixer and granulating same though the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60° C. for 12 hours the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

### Example 2

| | |
|---|---|
| Diltiazem Hydrochloride | 560 g |
| Crodesta F 160 | 59.5 g |
| Microcrystalline cellulose (Avicel pH 101) | 70 g |
| Povidone k 30 | 10.5 g |

The ingredients are introduced in a planetary mixer and dry mixed during approximately 15 minutes. There after 100 ml water USP is added and the mixing is pursued during 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spagetties". A spheronizer type caleva is used so as to transform the extruded product in beads. After drying during 12 hours, on trays, in an oven at 60° C. the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

### Example 3

Beads prepared in Example 1 were coated in a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technic. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter the coated beads were dried at 50° C. during 16 hours.

Coating suspension composition:

| | |
|---|---|
| Magnesium stearate | 12.5 g |
| Titanium dioxide | 5.0 g |
| Povidone k 30 | 5.0 g |
| Eudragit NE30D | 620.0 g |
| Talc USP | 17.5 g |
| water | 338.0 g |
| Simethicone | 1.0 g |
| Tween 80 | 0.8 g |

"In vitro" dissolution were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate butter pH 5.8 and the revolution speed 100 rpm.

| elapsed time [h] | percent dissolved [%] |
|---|---|
| 1 | 5 |
| 4 | 34 |
| 8 | 62 |
| 12 | 84 |

### Example 4

The beads as in Example 2 were coated using a fluidized bed coater equipped with a "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30–35 g per minute. Thereafter the coated beads were dried during 15 hours at 45° C.

Coating suspension:

| | |
|---|---|
| Magnesium stearate | 0.636 kg |
| Talc | 0.636 kg |

-continued

| | |
|---|---|
| Titanium dioxide | 0.0909 kg |
| Hydroxypropylmethylcellulose | 0.200 kg |
| Polysorbate 80 NF | 0.007 kg |
| Simethicone c emulsion | 0.018 kg |
| Eudragit NE 30 D | 12.4 kg |
| purified water | 6.7 kg |

Dissolution "in vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained of 37±0.5° C.

| elapsed time [h] | percent dissolved [%] |
|---|---|
| 2 | 9 |
| 4 | 33 |
| 6 | 54 |
| 8 | 82 |

Pharmacokinetical results

The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Pat. No. 4,721,619. (Cardizen SR®) therefore 6 healthy subject received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) during 7 days. At each of the eight day, 11 samples of blood were withdrawn when product of Example 4 was administered and 15 blood samples where withdrawn after the Cardizen SR® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. FIG. 1 shows the results obtained: the continuous line represent the Diltiazem plasma levels obtained with the product of Example 4 and the broken line the Diltiazem plasma levels of Cardizen SR®.

FIG. 1

Pharmacokinetical parameters:

| | Units | Example 4 | Cardizen SR ® |
|---|---|---|---|
| Area under the curve [0–24 h] | mg.h/ml | 2782 ± 1037 | 2864 ± 1222 |
| Maximal concentration | mg/ml | 116.3 ± 54.1 | 192.7 ± 85.3 |
| Time of maximum concentration | h | 8.0 ± 1.8 | 5.2 ± 2.8 |
| Fluctuation | % | 85.7 ± 25.7 | 109.5 ± 25 |
| Time during the concentration is above 75% of the maximum concentration | h | 9.8 ± 2.3 | 6.7 ± 3.7 |

From these results the following conclusion can be drawn:

First, FIG. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Second, the bioavailability, expressed by the areas under the curve of the 2 products, is equivalent (no statistical detectable difference).

Third, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizen SR® after a twice daily administration.

Fourth, the time during the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with product of the previous art when given twice daily.

Food effect study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross over study. Blood samples were obtained before and until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment at an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. FIG. 2 curves shows the mean plasma levels obtained when the product is taken without food and the dotted curve the mean plasma levels obtained when the product is taken with food.

FIG. 2

Pharmacokinetics parameter - product of Example 4

| | Units | Fasting | Food |
|---|---|---|---|
| Area under the curve (total | mg. h/ml | 1988 ± 119 | 1925 ± 109 |
| Mean residence time | h | 21.3 ± 0.7 | 19.9 ± 0.9 |
| $K_a$ | $h^{-1}$ | 0.283 ± 0.024 | 0.300 ± 0.027 |
| Maximum concentration | mg/ml | 100 ± 4.8 | 112 ± 5.9 |

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20% regarding area under the curve, mean residence time and maximum concentration. The larger interval obtained for $K_a$ was due to the higher variability of this parameter, the difference between the treatment means remaining small (6.%).

From all the results it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the one obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract

or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant,

and wherein the wetting agent is selected from the group consisting of sugars, $C_{12}$-$C_{20}$ fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

2. The composition of claim 1, wherein the wetting agent is a sugar.

3. The composition of claim 1, wherein the effective amount of the wetting agent is about 8% by weight of the composition.

4. The composition of claim 1, wherein the wetting agent is sucrose stearate, the water-soluble or water-dispersible polymer or copolymer is hydroxypropylmethyl-cellulose and the water, acid- and base- insoluble polymer is an acrylic polymer.

* * * * *